Ropivacaine plasma concentrations after thoracic epidural anaesthesia

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Abstract

Introduction: The pharmacokinetic profile of ropivacaine varies according to the site of administration. The aim of this study was to determine ropivacaine plasma concentrations after thoracic epidural administration in patients undergoing abdominal surgery under combined epidural – general anaesthesia.
Material and methods: The study included 15 patients, aged 45-77 years, ASA I and II, scheduled for abdominal procedures, under combined epidural-general anaesthesia. Epidural was performed at T10-T11 or T11-T12 interspaces and all patients received 5 ml of ropivacaine 0.75% with fentanyl 100 µg. Blood samples were collected at 10, 40, 70, 100 and 130 min following ropivacaine administration. Determination of blood levels was achieved with high performance liquid chromatography.
Results: Mean ropivacaine plasma concentrations determined at 10, 40, 70, 100 and 130 min after epidural administration showed significant intersubject variation and were found to be 0.66±0.48, 0.43±0.26, 0.47±0.34, 0.40±0.2, 0.33±0.19 µg/ml, respectively. Peak plasma concentrations occurred 10 min after administration in 10 patients, at 40 min in one patient, at 70 min in 3 patients and at 100 min in 1 patient with a mean of 0.65±0.46 µg/ml (range 0.25-1.59 µg/ml). The terminal half-life determined in 12 of the 15 patients was roughly estimated to be between 60 and 245 min (mean ± SD = 122±55 min).
Conclusions: Thoracic epidural administration of 5 ml ropivacaine 0.75% achieved plasma concentrations of between 0.1-1.59 µg/ml with an elimination half-life of approximately 122±55 min.

Key words: ropivacaine, plasma levels, thoracic epidural.

Introduction

Local anaesthetics reversibly inhibit regional sensory nerve impulse conduction, and they have been proven extremely useful for peri- and post-operative pain management. Epidural anaesthesia that is restricted to the level of the low thoracic and lumbar region (T_5-L_4) results in a peripheral sympathetic blockade with vascular dilatation in the pelvis and lower limbs. The stress response to surgery which is characterized by hyper-activation of the sympathetic nervous system is blocked, especially in the splanchnic region [1]. Thus combined epidural/general anaesthesia provides optimal perioperative anaesthesia and analgesia in patients undergoing major

abdominal surgery and decreases postoperative morbidity and mortality [2, 3].

The pharmacokinetic characteristics of the local anaesthetic ropivacaine (1-propyl-2',6'-pipecoloxylidide hydrochloride) have been assessed extensively in humans after epidural injection (20 ml 0.75% in patients undergoing orthopaedic procedures) [4]; extradural injection (20 ml 0.75% for caesarean section) [5]; epidural infusion (2.5 mg/ml for labour pain relief) and continuous epidural infusion (10 ml/h 0.1, 0.2, or 0.3%) for 21 h in healthy volunteers for post-operative pain relief [6]. In all these studies ropivacaine was administered through a lumbar epidural catheter.

The aim of this study was to determine the plasma concentrations achieved after epidural administration of 5 ml 0.75% ropivacaine in the thoracic region of the spinal cord, in patients undergoing major abdominal surgery under combined epidural/general anaesthesia.

Material and methods

Patients

This study protocol was approved by the Institutional Research and Ethics Committee, and written informed consent was obtained from all participants. The study included 15 patients enrolled consecutively, aged 45-77 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled for procedures of upper and lower abdomen, under combined epidural/general anaesthesia. Exclusion criteria included: ASA physical status > II, cardiac arrhythmias, liver or renal impairment, hypersensitivity to amide local anaesthetics, and common contraindications for performing regional anaesthesia, such as neuromuscular disease, bleeding diathesis and local skin infections of the thoracic area.

Anaesthetic procedures

All patients were premedicated with ranitidine 50 mg, and metoclopramide 10 mg intravenous (*i.v.*), 30 min before anaesthesia. Following iv prehydration with 500 ml of lactated Ringer's solution, epidural anaesthesia was performed at T_{10}-T_{11} or T_{11}-T_{12} interspaces (with the patient in the sitting position), with a Tuohy 18 G epidural needle (Portex Ltd. CT21 6JL, UK) using the loss of resistance technique with air. A multi-orifice epidural catheter was advanced 3 cm in a cephalic direction into the epidural space, and an epidural test dose of lidocaine 2% 3 ml was given after negative aspiration for cerebrospinal fluid or blood. Five minutes after the injection of the test dose and confirmation of the epidural position of the catheter, 5 ml of ropivacaine 0.75% (37.5 mg) was administered slowly at a rate of 0.5 ml/s, in addition with fentanyl 100 µg. After determination of the sensory level of analgesia (assessments were performed at 5 min intervals for the first 25 min using the pinprick method), general anaesthesia was induced with midazolam 0.02 mg/kg, thiopental sodium 5 mg/kg, fentanyl 2 µg/kg and rocuronium bromide 0.6 mg/kg *i.v.* After intubation of the trachea, patients were mechanically ventilated with a tidal volume of 6-8 ml/kg and a respiratory rate which were adjusted according to end tidal CO_2 values (35-40 mm Hg). Maintenance of anaesthesia was achieved with isoflurane 0.6-1%, in O_2/N_2O (40/60%) and incremental doses of rocuronium bromide according to train-of-four indications. Additional incremental *i.v.* doses of fentanyl were also used, depending on patients' analgesic requirements.

Monitoring consisted of invasive arterial pressure and CVP measurement, ECG, $ETCO_2$, SpO_2 (Datex-Ohmeda, 5250 RGM, Louisville, USA), neurostimulator, as well as urine output measurement. Hypotension was defined as a decrease in systolic blood pressure by more than 30% of the pre-anaesthetic value and was treated with ephedrine 5 mg *i.v.* and fluid administration, while bradycardia (<50 bpm) was treated with atropine 0.5 mg *i.v.*

Moreover, side effects of local anaesthetics such as seizures, arrhythmia or allergic reactions, and early complications of the epidural technique (dural perforation, subarachnoid injection, intravascular injection, total spinal anaesthesia, subdural spread) were recorded during the observation period.

Timing and assay of blood samples

Blood samples were collected before and 10 min after epidural administration of ropivacaine, and then every 30 min. The last blood sample was collected 130 min after ropivacaine administration. All blood samples were collected from an antecubital vein in the arm (contralaterally to the arm used for drug and fluid infusions), stored in heparinized tubes and immediately centrifuged. Plasma was stored at –70°C until the time of measurements.

The method of Reif et al. [7] was used in order to determine ropivacaine levels in plasma, with high performance liquid chromatography (HPLC). Calibration curves of ropivacaine were linear between 0.02 and 2 µg/ml and the limit of detection in plasma was 0.01 µg/ml with an inter-assay precision of 4-4.5%.

Statistical analysis

Ropivacaine concentrations measured were tabulated for each patient. Data were summarised as mean ± SD and range. The maximum plasma concentration (Cmax) and the time to reach Cmax (Tmax) were estimated directly from the individual plasma concentration-time curves. Rough estimates of terminal half-lives ($t_{1/2}$) were calculated as $\ln(2)/\lambda z$ following determination of the first order rate constant (λz) by log-linear regression of the terminal portion of the concentration-versus-time

curve (on the basis of the last three data points). Areas under the total plasma concentration-time curves (AUC) were calculated from the time of dosing to the time of the last observation by the linear trapezoidal method. The pharmacokinetic calculations were performed using the software package WinNonlin Professional version 3.1 (Pharsight Co., Mountain View, CA).

For statistical analysis, Kruskal-Wallis (nonparametric ANOVA) was used to study differences in ropivacaine plasma concentrations between patients, while the Spearman correlation test was used to evaluate the relation between ropivacaine concentrations and the age and weight of each patient: $P<0.05$ was considered statistically significant.

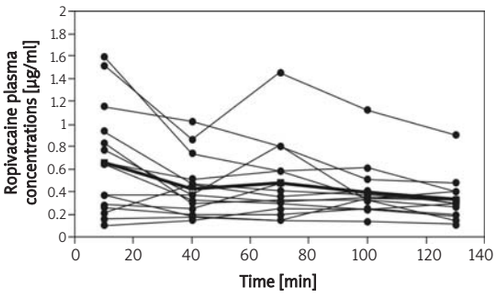

Figure 1. Individual plasma concentrations of ropivacaine 0.75% after thoracic epidural administration of 5 ml (37.5 mg) of the anaesthetic to patients undergoing abdominal surgery with combined epidural/general anaesthesia (n=15). The line in bold represents mean concentrations

Results

Fifteen patients participated in this study (11 women, 4 men), aged 45 to 77 years (mean 63.2, median 67). Demographic data and clinical characteristics of patients are summarized in Table I. The upper level of epidural analgesia achieved ranged between the T_6 and T_4 level. In the first 25 min after epidural administration no correlation was found between the sensory level of analgesia using the pinprick method and ropivacaine plasma concentrations (mean/peak). Thirteen patients had cardiovascular stability throughout the procedure (arterial pressure and heart rate within 10-30% of baseline values), while 2 patients had bradycardia and were treated with atropine (patients 2 and 9). No early complications due to epidural technique were observed.

Ropivacaine plasma concentrations achieved in the study patients were 0.65±0.46, 0.42±0.25, 0.47±0.34, 0.39±0.22 and 0.33±0.19 µg/ml at 10, 40, 70, 100 and 130 min, respectively (see Figure 1). Significant inter-subject variation in plasma concentrations was noted ($P<0.001$). The highest plasma concentrations of ropivacaine after epidural injection were observed 10 min after administration in 10 patients, at 40 min in one patient, at 70 min in three patients and at 100 min in one patient, with a mean of 0.65±0.46 µg/ml (range 0.25-1.59 µg/ml). In one patient the last two measured ropivacaine concentrations were higher than the previous three (patient 1). In this patient and two others (patients 11, 14) ropivacaine concentrations would not allow

Table I. Demographic and clinical characteristics of patients participating in the study

Patient code No.	Sex	Age [years]	Weight [kg]	Height [cm]	ASA physical status	Type of surgery
1	Female	71	82	162	2	Pelvis tumour resection
2	Male	67	80	180	2	Pelvis tumour resection
3	Female	63	60	153	2	Liver tumour resection
4	Male	67	65	169	2	Pancreas tumour resection
5	Female	47	92	164	1	Liver tumour resection
6	Female	68	72	164	2	Intrauterine tumour resection
7	Female	65	67	160	2	Intrauterine tumour resection
8	Female	45	78	170	2	Pelvis tumour resection
9	Female	63	44	144	2	Pelvis tumour resection
10	Male	77	78	175	2	Pelvis tumour resection
11	Female	69	73	163	2	Pelvis tumour resection
12	Female	70	69	166	2	Pelvis tumour resection
13	Female	57	66	160	2	Pelvis tumour resection
14	Female	49	64	156	2	Pelvis tumour resection
15	Male	71	65	170	2	Pelvis tumour resection

ASA – American Society of Anesthesiologists physical status classification

Table II. Pharmacokinetic data for ropivacaine 0.75% after thoracic epidural administration of 5 ml (37.5 mg) of the anaesthetic to patients undergoing abdominal surgery under combined epidural/general anaesthesia (n=12)

Patient	Tmax [min]	Cmax [µg/ml]	AUC [µg/ml/min]	$t_{1/2}$ [min]
2	40	0.46	45.5	192
3	70	0.47	43.4	93
4	70	0.30	30.7	103
5	10	1.15	100.1	81
6	10	1.59	95.7	112
7	10	0.66	60.6	63
8	10	0.83	48.9	245
9	10	0.93	60.9	168
10	10	1.51	146.6	87
12	10	0.37	39.4	60
13	10	0.37	22.9	134
15	70	0.25	23.9	127
Mean		0.74	59.9	122
SD		0.47	36.9	55

SD – standard deviation, Cmax – concentration corresponding to Tmax, Tmax – time of maximum observed concentration, AUC – area under the concentration/time curve from the time of dosing to the time of the last observation, $t_{1/2}$ – terminal half life (Winnonlin Nonlinear Estimation Program)

estimation of the terminal half-life from the first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve, i.e. using the last three data points; thus rough estimates of ropivacaine pharmacokinetic parameters ($t_{1/2}$ and AUC) included data from 12 patients only. Pharmacokinetic parameter estimations are shown in Table II. The age, weight, and maximum plasma levels of the study patients were studied to determine possible correlations between these variables, but no significant correlation was observed.

No serious adverse effects concerning cardiovascular or central nervous system (CNS) toxicity of ropivacaine were reported in this study.

Discussion

The character of anaesthesia and analgesia after epidural administration is dependent on the volume, concentration, and dose of local anaesthetic administered. The dose of local anaesthetic in the thoracic region is 15-30% lower than that in the lumbar region, i.e. 0.5-0.8 ml per segment (approximately an average volume of 5-7 ml has to be infused via the lower thoracic interspaces to achieve T_4 level of epidural analgesia) [8].

In the current study significant inter-subject variation in ropivacaine plasma concentrations following thoracic epidural injection of 5 ml 0.75% (37.5 mg) of the local anaesthetic was observed [P<0.001, Kruskal-Wallis (nonparametric ANOVA)]. Maximum plasma concentrations occurred 10 min after administration in 10 patients, at 40 min in one patient, at 70 min in 3 patients and at 100 min in 1 patient, and ranged between 0.25 and 1.59 µg/ml with a mean of 0.65±0.46 µg/ml. No significant correlation was observed between the age, weight, and maximum plasma concentrations of the study patients. The terminal half-life was roughly estimated to be between 60 and 245 min [122±55 min (mean ± SD)] for 12 of the 15 patients. The pharmacokinetic parameters estimated in previous studies after epidural administration of 0.5-0.75% ropivacaine (20-28 ml or 140-187 mg) in the lumbar region for elective caesarean section were found to be in the range 1.0-1.6 µg/ml for Cmax, 0.12-0.4 l/h for Cl and 2.5-9.4 h for $t_{1/2}$ [5, 9-12]. The plasma concentration of local anaesthetics after epidural anaesthesia depends on the total dose injected at each site of administration and is not noticeably affected by alteration of the concentration of the injection [13]. Emanuelsson et al. 1997 [14] and Sandler et al. 1998 [15], whose studies included comparisons of three different doses of ropivacaine (20, 40 and 80 mg *i.v.* infusion) in healthy volunteers and 125, 187.5 and 250 mg (25 ml epidural bolus) during hysterectomy, observed that the Cmax and AUC of ropivacaine increased proportionally with the dose, whereas apparent CL and $t_{1/2}$ were similar for all three doses in each study. Our study gave similar estimations of $t_{1/2}$ and clearance to those found after administration in the lumbar region, and as expected a lower Cmax due to the smaller ropivacaine dose administered, but also possibly due to the different anatomic region for epidural injection (thoracic).

Although local anaesthetics do not depend on circulation to reach their site of action, systemic uptake is largely responsible for the duration of their action, as well as the potential for systemic toxicity and adverse effects. Venous plasma concentrations ranging from 1 to 2 µg/ml following *i.v.* administration of ropivacaine in unpremedicated volunteers were found to produce mild CNS symptoms [16]. Local anaesthetic toxicity was not observed in other studies in which patients, premedicated with benzodiazepines, had even higher plasma concentrations of ropivacaine [17, 18]. Knudsen et al. (1997) reported a threshold for CNS toxicity (maximum tolerated doses 85-160 mg, arterial unbound ropivacaine concentration 0.6 µg/ml) [19]. In the present study, thoracic epidural administration of 5 ml ropivacaine 0.75% (37.5 mg) did not produce concentrations above 1 µg/ml in 12 of the 15 patients, while in the remaining 3 patients concentrations did not exceed 1.59 µg/ml. Moreover, in patients 6 and 10 (with Cmax values of 1.59 and 1.51 µg/ml, respectively within 10 min) no

adverse CNS effects were observed, despite the fact that general anaesthesia had not yet been induced to cover signs of CNS toxicity. Furthermore, in the current study benzodiazepines were not administered as premedication before epidural anaesthesia, but during induction of general anaesthesia 25 min later.

In conclusion, our findings indicated that local anaesthetic plasma concentrations after thoracic epidural anaesthesia with 5 ml of ropivacaine 0.75% (37.5 mg) peaked 10 min after epidural administration in 66% of patients studied, giving mean (N=15) maximum ropivacaine concentration of 0.65±0.46 µg/ml. The elimination half-life of ropivacaine was roughly estimated to be 122±55 min in 12 of the 15 study patients. Also, no adverse effects were observed regarding CNS or cardiac toxicity with these plasma concentrations of ropivacaine. However, significant inter-subject variation in ropivacaine plasma levels indicate that more studies are needed to investigate ropivacaine's pharmacokinetic profile after administration into different regions of the epidural space. Moreover, limitations of our study were the patients' ASA status, the "single-shot" epidural injection, the standard ropivacaine dose and the duration of the postoperative observation period. Further investigations are needed to study the pharmacokinetic characteristics of ropivacaine after repeated thoracic epidural administrations or after continuous epidural infusion administered in the thoracic region.

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